Protocol Title: Phase II trial of XmAb20717 in patients with advanced biliary tract cancers

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CLINICAL RESEARCH PROTOCOL

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PROTOCOL(S) TITLE:		Phase II trial of XmAb20717 in patients with advanced biliary tract cancers
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REGULATORY SPONSOR:		Mark O'Hara, MD University of Pennsylvania Perelman School of Medicine Perelman Center for Advanced Medicine 3400 Civic Center Boulevard, South Tower, Floor 10 Philadelphia, PA 19104
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PRINCIPAL INVESTIGATOR SIGNATURE

STUDY SPONSOR:	Mark O'Hara, MD
STUDY TITLE:	Phase II trial of XmAb20717 in patients with advanced biliary tract cancers
STUDY ID	UPCC 17221 (PennIRB#850515)
PROTOCOL VERSION	8.0

I have read the referenced protocol. I agree to conduct the study in accordance to this protocol, in compliance with the Declaration of Helsinki, Good Clinical Practices (GCP), and all applicable regulatory requirements and guidelines.

Principal Investigator Name _____ Signature _____

Affiliation: _____ Date _____

Abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
BTCs	Biliary tract cancers
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
Cmax	Maximal concentration
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CrCl	Creatinine clearance
CRF	Case Report Form
CTLA4	Cytotoxic T-lymphocyte associated protein
DOR	Duration of response
eCRF	Electronic Case Report Forms
Fab	Fragment, antigen binding
Fc	Fragment, crystallizable
FcRn	Neonatal Fc receptor
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFP	Fresh frozen plasma
GAP	Gemcitabine, nab-paclitaxel(abraxane), and cisplatin
GCP	Good Clinical Practice
GemCis	Gemcitabine and cisplatin
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonization
iCPD	iRECIST confirmed progressive disease
iCR	Complete response by iRECIST
IgG	Immunoglobulin G
IND	Investigational New Drug Application
INR	International normalized ratio
iPR	Partial response by iRECIST
irAEs	Immune related adverse events
IRB	Institutional Review Board
iSD	Stable disease by iRECIST
iUPD	iRECIST unconfirmed progressive disease
LLN	Lower limit of normal
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD1	Programmed cell death receptor 1
PI	Principal Investigator

PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
scFγ	Single-chain variable fragment (immunoglobulin fusion protein)
SoA	Schedule of Activities
ULN	Upper limit of normal
UP	Unanticipated Problem

1 STUDY SUMMARY

1.1 Synopsis

Title:	Phase II trial of XmAb20717 in patients with advanced biliary tract cancers
Short Title:	XmAb20717 in advanced BTCs
Study Description:	This is a single-arm, phase II clinical trial to evaluate the efficacy of XmAb20717 in patients with advanced biliary tract cancers who have progressed on, or were intolerant of, a gemcitabine-based chemotherapy regimen.
Objectives:	*Primary Objective:* To assess efficacy, in terms of ORR, of XmAb20717 when used to treat patients with advanced biliary tract cancers who have progressed on, or were intolerant of, a gemcitabine-based chemotherapy regimen. *Secondary Objectives:* To assess efficacy and safety in terms of PFS, ORR by iRECIST, DOR, OS, and incidence of AE's in patients treated with XmAb20717 with advanced biliary tract cancers who have progressed on, or were intolerant of, a gemcitabine-based chemotherapy regimen. To assess the ORR within subgroups of patients defined by patients who have or have not received immune checkpoint inhibitor therapy prior to study enrollment. *Exploratory Objectives:* To assess for the presence of biomarkers predictive of treatment response using pre- and optional post-treatment biopsies for tumor next generation sequencing, gene-expression profiling, and tumor IHC for immune cell markers; and using serial peripheral blood analysis for circulating immune cells using multi-parameter flow-cytometry.
Primary Endpoint:	ORR is the primary endpoint and is defined per RECIST 1.1, representing the proportion of patients with best response being complete response (CR) or partial response (PR).
Secondary Endpoints:	PFS is a secondary endpoint and is defined as time from study enrollment until disease progression or death with censoring for loss to follow up. ORR by iRECIST is assessed using the guidelines outline in section 8.3.5.3. OS is an additional secondary endpoint and is defined as time from study enrollment until death

	with censoring for loss to follow up. DOR is a secondary endpoint and is defined as time from measurement criteria being met for CR or PR (whichever is first recorded) to the first date that recurrent or progressive disease is objectively documented (taking as a reference for progressive disease the smallest measurements since the treatment started). Proportion of patients experiencing AEs on experimental therapy will be a secondary endpoint and will be categorized per CTCAE version 5.0. The secondary endpoint of ORR within subgroups of patients defined by receipt of prior immunotherapy will be defined in the same way as for the primary endpoint. Exploratory endpoints will include correlative endpoints. Tumor cell infiltrate will be assessed by IHC for immune cell markers and scored as number of cells expressing each marker per 40X field. Gene expression profiling will be performed on tumor tissue by RNAseq and each gene will be normalized to a standard, stably expressed gene. Multiparameter flow cytometry will be performed on peripheral blood and the number of cells expressing immune cell markers of interest will be expressed as cells per unit volume and as a percent of circulating mononuclear cells examined.
Study Population:	The study population will consist of 27 evaluable adult patients with advanced biliary tract cancer treated at the Abramson Cancer Center who have progressed, or were intolerant of, a gemcitabine-based chemotherapy regimen.
Phase:	Phase II
Description of Sites/Facilities	The study will take place at the Abramson Cancer Center at the University of Pennsylvania.
Enrolling Participants:	This is a single-site study at the Abramson Cancer Center at the University of Pennsylvania.
Description of Study Intervention:	Study participants will receive the recommended phase II dose (10mg/kg) of XmAb20717 by intravenous infusion on days 1 and 15 of a 28-day cycle.

Study Duration:	30 months
Participant Duration:	From enrollment until disease progression, unacceptable toxicity, or withdrawal of consent. Otherwise, investigational treatment will be discontinued after two years if patient has not otherwise met criteria for treatment discontinuation. Patients who have completed two years of treatment without disease progression or unacceptable toxicity and experience disease progression after treatment discontinuation may undergo re-treatment with the investigational treatment.

1.2 Key Roles and Study Governance

Sponsor	Medical Director
Mark O'Hara, MD, Assistant Professor of Medicine	Mark O'Hara, Assistant Professor ofMedicine
Abramson Cancer Center at the University of Pennsylvania	Abramson Cancer Center at the University of Pennsylvania
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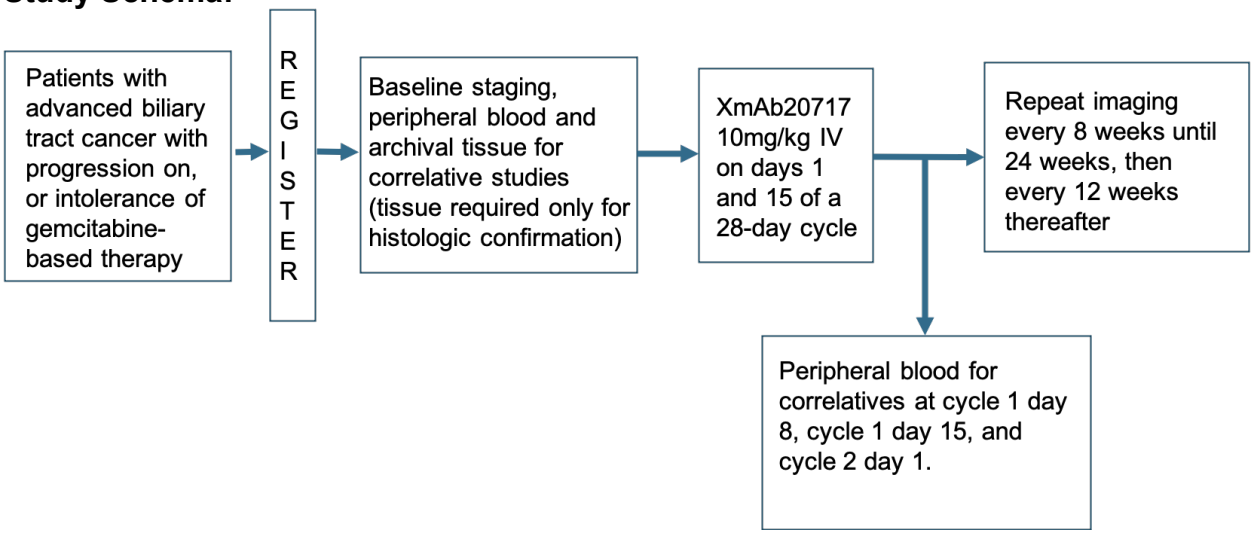
1.3 Schema

Study Schema:



2 INTRODUCTION AND RATIONALE

2.1 Study Rationale

Biliary tract cancers (BTCs) are responsible for more than 7,000 deaths per year in the United States, and they are among the fastest growing causes of cancer death in the country.[1] Estimated mortality due to BTCs has more than doubled in the past decade.[2] More than two-thirds of patients present with advanced disease that is not amenable to curative-intent surgery, and the mainstay of treatment for such patients is chemotherapy.[3] Initial treatment with gemcitabine and cisplatin (GemCis) provides a median progression-free survival (PFS) of 8.0 months and median overall survival (OS) of 11.7 months, while a triplet regimen adding nab-paclitaxel to GemCis (GAP) demonstrated a promising PFS of 11.8 months and OS of 19.2 months in a phase II trial.[4,5] Except for the minority of patients with targetable alterations such as mismatch repair deficiency (2%) or FGFR2 fusions (10-15% of intrahepatic cholangiocarcinoma), systemic treatment beyond 1st line chemotherapy has very limited efficacy, with standard therapy using 5-fluorouracil plus oxaliplatin (FOLFOX) increasing median overall survival less than one month (6.2 vs. 5.3 months) compared to active symptom control in the ABC-06 study.[67]

The activity of PD-1 and PD-L1 inhibitors for microsatellite stable BTCs has been largely disappointing, with response rates of 3-7% in the largest phase II trials.[8–10] Combination therapy with PD-1/L1 inhibitors and CTLA-4 inhibitors, however, has proven more promising, with response rates of 10.8% with durvalumab plus tremelimumab and 23% with nivolumab plus ipilimumab.[10,11] The activity of dual checkpoint blockade has also been demonstrated with chemoimmunotherapy combinations.

Xencor has developed a novel bispecific antibody targeting PD-1 and CTLA-4, XmAb20717, which has demonstrated activity in treatment-refractory solid tumors.[14] We propose a single-arm phase II trial of XmAb20717 in patients with advanced BTC previously treated with gemcitabine-based chemotherapy to evaluate efficacy.

2.2 Background

2.2.1 Therapeutic Bispecific Antibodies

The concept of recombinant antibodies that could bind two targets was developed in the late 1990s, but technical obstacles slowed development until recently. Now, advances in protein biology and recombinant expression techniques have led to several different formats for bispecific antibodies, each with different properties.[15] Bispecific antibodies allow for simultaneous engagement with two targets, potentially increasing binding specificity, providing dual activation or blockade of two disease mediators simultaneously, or, in the case of cancer therapy, providing the blockade of two immune checkpoint inhibitors simultaneously.

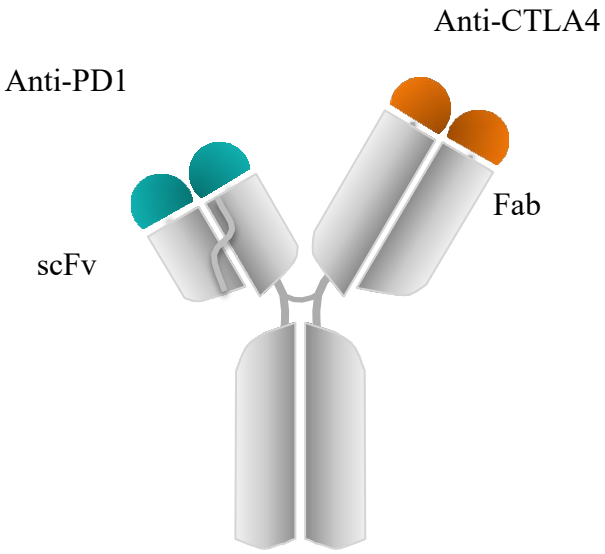
One limitation of several bispecific antibodies in development for oncology is that they are small and lack a full-fragment, crystallizable (Fc) region; they are therefore excreted rapidly from the body. Thus, they must be administered by continuous infusion if efficacious concentrations are to be maintained in the body.[16] For ease of use, a larger construct with pharmacokinetics (PK) similar to that of humanized antibodies would, therefore, be preferable because it should allow intermittent administration on a weekly or biweekly basis.

2.2.2 XmAb20717 Investigational Product Description

XmAb20717 is a humanized bispecific antibody that binds the immune checkpoint molecules PD-1 and CTLA4 in order to block signaling that prevents activated T cells from attacking and clearing tumor cells from the body.

XmAb20717 has been designed to maintain full-length humanized monospecific antibody properties in a bispecific, enabling the design of stable molecules with favorable in vivo half-life and allowing for the use of standard antibody production methods. To generate XmAb20717, Xencor humanized and affinity optimized anti-PD-1 and anti-CTLA4 antibodies and combined them in a single bispecific molecule. XmAb20717 is produced as a 3-chain scFv-Fab-Fc antibody (Figure 1) in which the single chain variable fragment (scFv) domain targets PD-1 and the fragment, antigen-binding (Fab) domain targets CTLA4. The neonatal Fc receptor (FcRn) affinity has been increased via amino acid engineering to improve serum half-life relative to antibodies containing native immunoglobulin G (IgG) Fc domains.

Figure 1: Schematic of XmAb20717 PD1 x CTLA4 Bispecific Monoclonal Antibody



CTLA4 = cytotoxic T-lymphocyte-associated protein; Fab = fragment, antigen binding; Fc = fragment, crystallizable; FcRn = neonatal Fc receptor; PD1 = programmed cell death protein 1; scFv = single-chain variable fragment (immunoglobulin fusion protein).

2.2.3 Human Experience with XmAb20717 and Similar Molecules

XmAb20717 is a bispecific antibody that binds both PD-1 and CTLA4. Although no bispecific antibody that simultaneously targets both these checkpoint pathways has been approved for marketing, the validity of the targets for the treatment of cancer has been confirmed in numerous clinical trials and by FDA approval of six monoclonal antibodies targeting the PD-1/PD-L1 pathway and one monoclonal antibody targeting the CTLA4 pathway in numerous oncologic indications.[17–23] In addition, combination anti-PD1/anti-CTLA4 therapy has received FDA approval for treatment of multiple advanced tumor types.[21,23]

Throughout the clinical trials of approved and newer checkpoint inhibitors targeting either the PD-1/PD-L1 or CTLA4 pathways, a characteristic and reasonably consistent safety profile has emerged that counts immune-related adverse events (irAEs) among the most frequent and consequential AEs. While almost any bodily system may be affected by drug-related autoimmune reactions, the most common irAEs have been skin toxicities, arthritis, and fatigue, and the most serious have been autoimmune pneumonitis, colitis, hypothyroidism/thyroiditis, pancreatitis, hepatitis, hypophysitis, adrenal insufficiency, nephritis/renal dysfunction, myocarditis, and diabetes.[24] In clinical trials of combination therapies that target the PD-1/PD-L1 and CTLA4 pathways simultaneously, the

incidences of some types of irAEs may differ from those observed with single therapy, but the types of irAEs have been very similar to those seen with single checkpoint therapy.

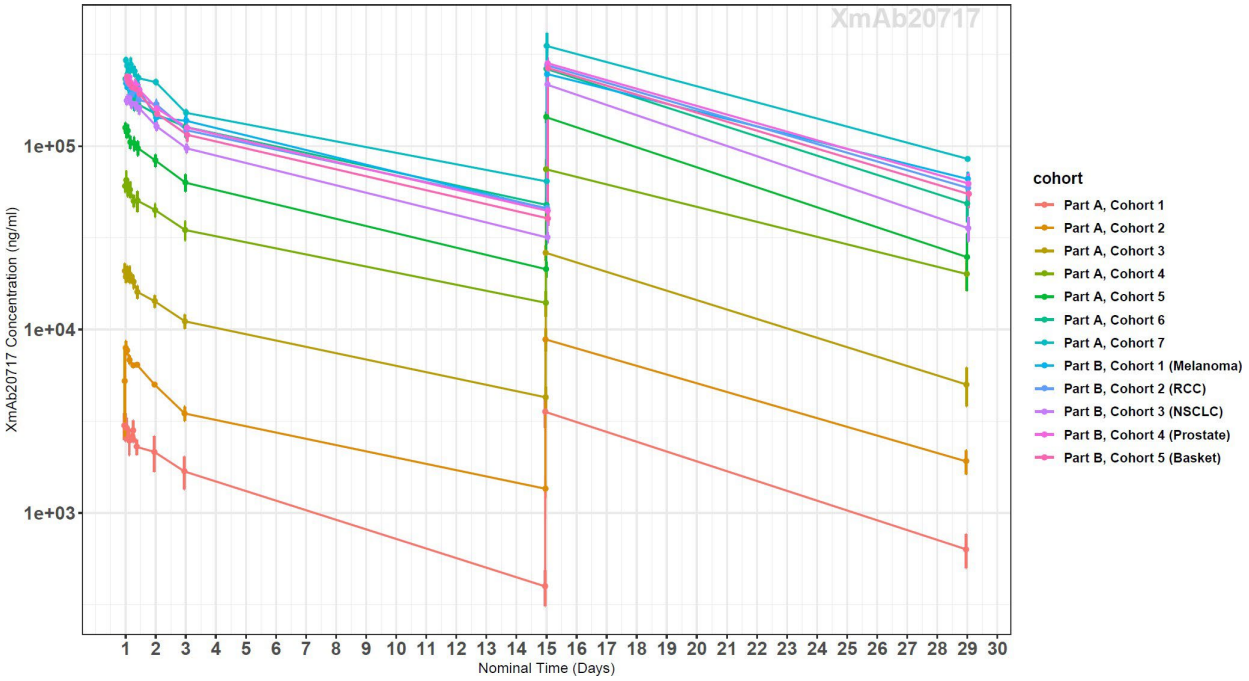
2.2.3.1 XmAb20717 Initial Clinical Experience in a Phase I Dose Escalation Study

To date, XmAb20717 has been evaluated in a single, ongoing, Phase 1, first-in-human, two-part dose-escalation and expansion trial in adults with selected advanced solid tumors (Study XmAb20717-01). Part A was a standard 3 + 3 dose escalation designed to define a maximum tolerated dose, recommended dose, and regimen; to assess safety and tolerability; to assess PK and immunogenicity; and preliminarily to assess potential antitumor activity of XmAb20717 in subjects with selected advanced solid tumors. In Part A, subjects were enrolled sequentially in up to 8 dose-level cohorts (ranging from 0.15 to 20.0 mg/kg Q2W) of up to 6 subjects each. Part B included treatment of up to 20 subjects each at the maximum tolerated dose or a recommended dose in the following cohorts: advanced melanoma, renal cell carcinoma (clear cell predominant type), non-small cell lung cancer, castrate-resistant adenocarcinoma of the prostate, checkpoint-inhibitor relapsed or refractory cutaneous melanoma, and a cohort of tumors for which there is published evidence of anti-tumor activity with anti-PD-1/L1 and/or anti-CTLA4-directed therapy but no FDA-approved anti-PD1/PD-L1 or anti-CTLA4-directed agents.

2.2.3.2 Pharmacokinetics

In PK data from Study XmAb20717-01 dose escalation and expansion cohorts, XmAb20717 demonstrated a dose proportional PK profile (Figure 2). Preliminary population pharmacokinetic analysis of XmAb20717 was performed on the PK data from 128 subjects. It was a two-compartmental linear model with a zero-order input (constant-rate infusion). Covariates in the model included baseline body weight and albumin level, and their effects on clearance and central volumes of distribution were modelled. Interindividual variability was estimated on the structural parameters using a full-block design and a proportional error model was used to describe the residual variability. Among subjects treated with 10 mg/kg Q2W, the mean values (standard deviation) of maximal concentration (Cmax) (µg/mL) and AUC (area under the curve) (h*µg/mL) were 225.5 (54.4) and 41823.0 (11549.2), respectively. The terminal half-life was estimated to be 12.3 days.

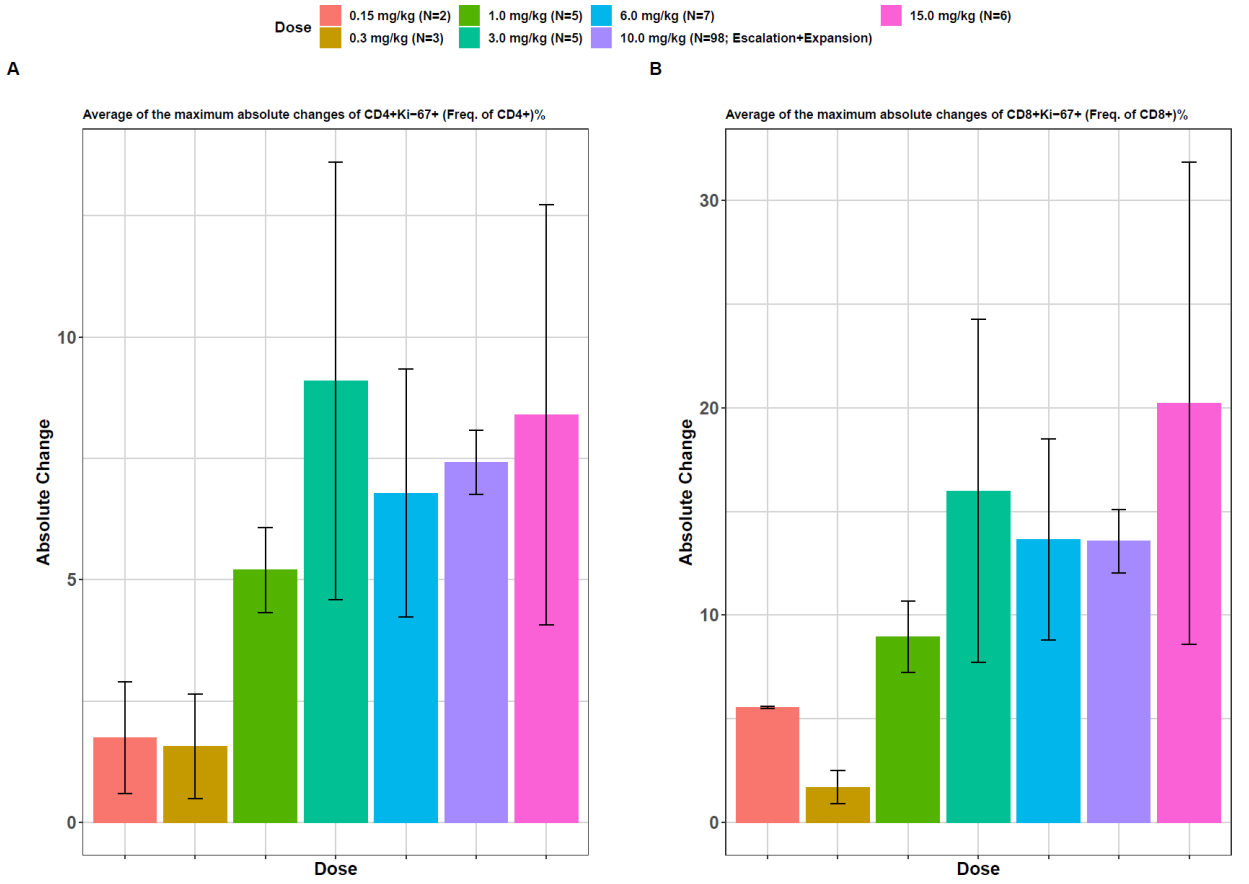
Figure 2: PK Profile for Dose Escalation and Expansion Cohorts in Study XmAb20717-01.



2.2.3.3 Pharmacodynamics

To evaluate peripheral blood pharmacodynamic activity of XmAb20717 in the dose escalation and expansion cohorts of Study XmAb20717-01, the proliferation marker ki67 was measured in T-cell subsets by flow cytometry. Increased T-cell proliferation, in both CD4 and CD8 T cells, was observed with increasing dose, consistent with dual checkpoint blockade. Figure 3 shows the average maximum absolute change in ki67+ T cells in the periphery through Cycle 2; peripheral pharmacodynamic responses generally peaked at Cycle 2 Day 1 and diminished thereafter. The highest absolute change was observed at the 10.0 and 15.0 mg/kg doses.

Figure 3: Peripheral Pharmacodynamic Activity: Maximum Absolute Change from Baseline in T-Cell ki67 (Percent of Total CD4 or CD8+ T cells)



2.2.3.4 Safety Data

A total of 145 subjects have been treated with XmAb20717 (safety population) in Study XmAb20717-01 as of May 10, 2021. Doses of 0.15 to 15.0 mg/kg IV have been administered Q2W in Part A without exceeding the maximum tolerated dose. A dose of 10 mg/kg Q2W was selected for expansion cohorts in Part B. Of all treated subjects, the majority (110) have been treated at the 10mg/kg dose level.

The most frequently reported treatment emergent adverse events (reported for >20% of subjects) in this clinical trial were fatigue (42.1%), pruritus (30.3%), anemia (28.3%), rash maculo-papular (27.6%), pyrexia (23.4%), and nausea (22.1%). The majority of treatment emergent adverse events considered related to the study drug in XmAb20717-01 are consistent with irAEs, which were reported in 75.5% of 110 subjects in the 10mg/kg dose group. The most frequently reported irAEs overall (reported for > 10% of subjects) were pruritus (26.9%), maculo-papular rash (25.5%), diarrhea (11.7%), rash (11.7%), and aspartate aminotransferase elevation (11.0%). The most frequent grade 3 or higher irAEs were maculo-papular rash (12.6%), acute kidney injury (3.9%), alanine aminotransferase

elevation (3.9%), aspartate aminotransferase elevation (3.9%), hyperglycemia (3.9%), and lipase elevation (3.9%). Grade 5 irAEs were reported for 2 subjects and included immune-mediated pancreatitis and myocarditis.

Immune-related adverse events that have been observed in XmAb20717-01 are consistent with the types of irAEs reported in clinical trials and post-approval treatment data for other PD-1/PD-L1 and CTLA4-directed checkpoint inhibitors. The events observed in XmAb20717-01 have included both more commonly identified irAEs, such as rash and pneumonitis, as well as rare, but previously reported, irAEs that have been associated with checkpoint inhibitor therapy, such as immune-mediated myocarditis and immune thrombocytopenia. Although the frequencies of some types of irAEs thus far observed with XmAb20717 are different from those reported for similar events in subjects treated with other anti-PD-1/PD-L1 and -CTLA4 checkpoint inhibitors, data for XmAb20717 are currently insufficient to determine the frequencies of specific irAEs with any degree of certainty. It is therefore not possible to determine at this time whether or not the safety profile of XmAb20717 is significantly different from the safety profile of similar agents.

2.2.3.5 Clinical Activity

At doses below 10mg/kg, best overall response was stable disease (SD). At 10mg/kg, best overall response was complete response (CR) in 1 subject and partial response (PR) in 9 subjects. The CR, observed in a subject with melanoma, was confirmed. PRs were observed in 2 subjects with melanoma, 2 subjects with renal cell carcinoma, 2 subjects with non-small cell lung cancer, 2 subjects with prostate cancer, and 1 subject with ovarian cancer.

2.2.4 Assessment for Potential Study Products Drug-Drug Interactions

There are currently no known or hypothesized drug-drug interactions with XmAb20717.

2.2.5 Clinical Adverse Event Profile

Immune-related adverse events that have been observed in XmAb20717-01 are consistent with the types of irAEs reported in clinical trials and post-approval treatment data for other PD-1/PD-L1- and CTLA4-directed checkpoint inhibitors as detailed in section 2.2.3.4.

2.2.6 Dosing Rationale

Dose escalation to 15mg/kg of XmAb20717 was performed in the XmAb20717-01 phase I study and no maximum tolerated dose was identified. As highlighted in Figure 3,

pharmacodynamic measures of CD4+ and CD8+ T cell expansion in response to treatment noted maximum increases with doses of 10mg/kg and 15mg/kg. Based on this data, 10mg/kg was determined to the recommended dose for the expansion cohorts in part B of the study. When clinical activity was assessed, no objective responses were observed at doses of less than 10mg/kg, while 1 CR and 9 PRs (ORR 21.3%) were observed at the 10mg/kg dose with acceptable toxicity profile. On this basis, 10mg/kg IV on days 1 and 15 of a 28 day cycle will be the doses evaluated in the present study.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Current understanding of the risks associated with XmAb20717 in humans is based on preliminary data from 145 subjects with selected advanced solid tumors treated in an ongoing Phase 1 study (XmAb20717-01). Adverse events observed following treatment with XmAb20717 in this study were predominantly irAEs that are consistent with the types of irAEs reported in clinical trials and post-approval treatment data for other PD-1/PD-L1- and CTLA4-directed checkpoint inhibitors. Additional detail is included in section 2.2.3.4.

2.3.2 Known Potential Benefits

As the current standard of care treatment (FOLFOX) after progression on, or intolerance of, gemcitabine based chemotherapy demonstrated only a 5% ORR and a marginal 1 month increase in OS compared to best supportive care,[7] the current research protocol offers the potential benefit of improved disease control. In the phase I XmAb20717-01 study at the 10mg/kg dose, best overall response was complete response (CR) in 1 subject with melanoma and partial response (PR) in 9 subjects (ORR of 21.3% among evaluable subjects), including subjects with melanoma, renal cell carcinoma, non-small cell lung cancer, prostate cancer, and ovarian cancer. Responses to immunotherapy are often durable and can substantially prolong survival in those with an objective response. Only one patient with cholangiocarcinoma was included in this study and was treated at the 10mg/kg dose, and did not experience a CR or PR to treatment.

2.3.3 Assessment of Potential Risks and Benefits

As the risk associated with XmAb20717 appear proportional to the risks of FDA approved combination therapies with PD-1/PD-L1 and CTLA-4 check point inhibitors and the study treatment has the potential to improve disease response and disease control compared to an inadequate standard of care, the risk-benefit ratio favors participation in the study. Risks were minimized in the design of the study as patients with a higher likelihood of toxicity with immunotherapy, including active auto-immune conditions, are excluded from participation in the study. Additionally, the design of the study ensures that patients have

progressed on, or were intolerant of, effective first-line therapy for advanced biliary tract cancers which consists of gemcitabine-based chemotherapy.

3 STUDY OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To assess efficacy, in terms of best overall treatment response (ORR), of XmAb20717 when used to treat patients with advanced BTCs who have progressed on, or were intolerant of, a gemcitabine-based chemotherapy regimen.	ORR is the primary endpoint and is defined per RECIST 1.1, representing the proportion of patients with best response being complete response (CR) or partial response (PR). The primary endpoint for ORR will be met if 4 or more responses are observed in 27 evaluable patients indicating a significantly higher ORR than a null ORR of 5%.	This degree in improvement in ORR would be clinically meaningful and would support further investigation of XmAb20717 in this patient population.
Secondary		
To assess efficacy and safety, in terms of ORR by iRECIST, PFS, DOR, OS, and incidence of AEs in patients treated with XmAb20717 with advanced BTCs who have progressed on, or were intolerant of, a gemcitabine-based chemotherapy regimen. To assess the ORR within subgroups of patients defined by patients who have or have not received immune checkpoint inhibitor therapy prior to study enrollment.	ORR by iRECIST is defined in section 8.3.5.3. PFS is defined as time from study enrollment until radiographic disease progression per RECIST 1.1 or death, with censoring for loss to follow up. OS is defined as time from study enrollment until death, with censoring for loss to follow up. DOR is defined as time from first treatment response to progression or death and will only be evaluable in patients with CR or PR to therapy. Proportion of patients experiencing AEs on experimental therapy will be a secondary endpoint and will be categorized per CTCAE version 5.0. The exploratory endpoint of ORR within subgroups of patients defined by receipt of prior immunotherapy will be defined in the same way as for the primary endpoint.	Secondary endpoints will be descriptive and will allow for characterization of clinical efficacy and safety in terms of patient important outcomes. The assessment of ORR within subgroups of patients defined by receipt of prior immune checkpoint inhibitor therapy will help to characterize efficacy of the XmAb20717 in the growing population of patients who will receive immune checkpoint inhibitor therapy in the first-line setting.
Tertiary		

To assess, in an exploratory fashion, for the presence of biomarkers predictive of treatment response using pre-treatment biopsies for tumor next generation sequencing and tumor IHC for immune cell markers; and using pre- and post-treatment peripheral blood	Tumor cell infiltrate will be assessed by IHC for immune cell markers and will be scored as the number of cells expressing each marker per 40X field. Gene expression profiling will be performed on tumor tissue by RNAseq and each gene will be normalized to a standard, stably expressed gene. Multiparameter flow cytometry will be	Exploratory, correlative endpoints may result in definition of predictive biomarkers for treatment with XmAb20717 in this patient population and may provide additional information regarding

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
analysis for circulating immune cells using multi-parameter flow-cytometry.	performed on peripheral blood and the number of cells expressing immune cell markers of interest will be expressed as cells per unit volume and as a percent of circulating mononuclear cells examined. Intra-patient comparisons will be made pre- and post- treatment with XmAb20717 and inter-patient comparisons will be made between patients with treatment response and those without treatment response.	mechanisms of treatment response or resistance.

4 STUDY PLAN

4.1 Study Design

We hypothesize that XmAb20717 will be efficacious with a manageable toxicity profile when used for treatment of patients with advanced BTCs who have progressed on, or were intolerant of, gemcitabine-based systemic therapy. This is a phase II, single-arm trial using a Simon two-stage mini-max design with planned interim analysis for futility, as described in section 9.4.2, investigating XmAb20717 in patients with advanced BTCs who have progressed on, or were intolerant of, gemcitabine-based systemic therapy. The study intervention will consist of XmAb20717 administered intravenously at a dose of 10mg/kg on days 1 and 15 of a 28-day cycle. Therapy with XmAb20717 will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Patient enrollment will occur at a single site; the Abramson Cancer Center at the University of Pennsylvania.

4.2 Scientific Rationale for Study Design

A single-arm phase II trial evaluating the response to treatment with XmAb20717 compared to a historical null ORR of 5% is appropriate given the underwhelming second-line options available for patients with advanced BTCs that have progressed on, or were intolerant of, gemcitabine-based chemotherapy. The current standard of care option in this setting is FOLFOX from the ABC-06 trial, which increased median OS by 1 month compared to active symptom control and had an ORR of 5%.[6]

4.3 Justification for Dose

Based on the phase I XmAb20717-01 trial, the dose for XmAb20717 or 10mg/kg administered intravenously on days 1 and 15 of a 28 day cycle was selected as the recommended dose for further study as detailed in section 2.2.6.

4.4 Toxicity Management for Immune-Related Adverse Events

IrAEs may involve every organ or tissue.[25] Most irAEs occur within the first 12 weeks of exposure to an immune-checkpoint inhibitor, but some of them may appear with a delayed onset. Diagnosis of irAEs should be based on exposure to XmAb20717 and a reasonable immune-based mechanism of the observed AE. Whenever possible, histologic examination or other immune-based diagnostic evaluations should be used to support the diagnosis. Other etiologic causes, including AEs due to tumor progression, should be ruled out.

The spectrum of irAEs is wide and can be general or organ-specific. Examples of general irAEs in patients treated with immune-checkpoint inhibitors are fatigue, fever, and chills.

Organ-specific irAEs consist of pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, skin adverse reactions, encephalitis, myocarditis, and endocrinopathies.

Early recognition and management of irAEs associated with immune-oncology agents may mitigate severe toxicity. Medical management of irAEs should focus on suppressing the immune response with nonsteroidal and steroidal anti-inflammatory medication. Management algorithms, which provide guidelines on holding, rechallenging, and discontinuation of treatment, have been developed by the National Comprehensive Cancer Network (NCCN) (Appendix 12.2). The accurate diagnosis and subsequent treatment of irAEs are complex and not captured in any single guidance document, so the management of suspected irAEs is ultimately at the discretion of the treating investigator in consultation with the principal investigator. No dose modifications of XmAb20717 are permitted.

If treatment with XmAb20717 is withheld for management of immune checkpoint inhibitor-related toxicities, it should be held until the toxicity has returned to baseline or Grade ≤ 1. Exceptions to this guideline may be permissible if deemed appropriate by the principal investigator.

Patients with drug-related endocrinopathies controlled with hormone replacement such as insulin or adrenal replacement-dose steroids may resume treatment when toxicity has improved to Grade ≤ 1. Dose interruption is not required for hyper- or hypothyroidism but supportive care (e.g. thyroid replacement) should be started per institutional standards.

Corticosteroids are frequently indicated for Grade 3 or greater toxicities, and are necessary at times for lower grade toxicities. Guidance for their use and dosing is available in the NCCN guidelines for management of immune checkpoint inhibitor-related toxicities in Appendix 12.2.[24] For any toxicity of XmAb20717 (regardless of grade) that, despite optimal supportive care, is felt by the treating Investigator to present a risk to safety of the patient, additional treatment delay or treatment discontinuation is permitted

at the discretion of the treating Investigator.

4.5 End of Study Definition

A participant is considered to have completed the study if he or she has completed all phases of the study through the end of treatment visit shown in the Schedule of Activities (SoA), Appendix Section 12.1.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the study
3. Male or female, aged ≥ 18 years of age
4. Patient must have advanced BTC including intrahepatic, perihepatic, or extrahepatic cholangiocarcinoma or gallbladder carcinoma with histologic or cytologic confirmation who have experienced progression, or intolerance of, systemic therapy with a gemcitabine-based regimen.
5. Patients with tumors harboring an FGFR2 fusion, NTRK fusion, or IDH1 mutation must have received molecularly targeted therapy unless contraindicated or refused. Patients without sequencing results for FGFR2 fusions, NTRK fusions, or IDH1 mutations at the time of screening are permitted to enroll in the study. If sequencing results demonstrating FGFR2 fusions, NTRK fusions, or IDH1 mutations become available after patients have enrolled on the study, patients will be informed of the results and available treatment options but may continue study treatment if they are deriving clinical benefit.
6. ECOG performance status of 0 or 1.
7. Measurable or evaluable disease as defined by RECIST v. 1.1.
8. Available archival tissue or willingness to undergo biopsy during the screening period; this requirement can be waived if biopsy deemed infeasible or unsafe by the principal investigator
9. For females of reproductive potential: Must have a negative serum pregnancy test performed within 7 days of first study treatment and must agree to use such a method during study participation and for an additional 3 months after the last study dose of XmAb20717. Reproductive potential is defined in section 8.2.11.
10. For males of reproductive potential with female partners of reproductive potential (per section 8.2.11): Must use of condoms or other methods to ensure effective contraception with partner during the study and for an additional 4 weeks after the end of XmAb20717 administration as outlined in section 8.2.11. Male subjects must agree not to donate sperm from screening through 4 weeks after completion of study
11. Must have adequate organ and hematopoietic function within 14 days of the start of study treatment as defined in Table 1. Labs from cycle 1 day 1 may be used for

eligibility.

Table 1: Baseline Laboratory Parameters

Laboratory Test	Required Value
Absolute neutrophil count (ANC)	≥ 1.0 x 10^9/L
Platelet count	≥ 60,000 x 10^9/L
Hemoglobin	≥ 8.0 x 10^9/L
Alanine aminotransferase (ALT)	≤ 3xULN (or 5xULN with liver involvement)
Aspartate aminotransferase (AST)	≤ 3xULN (or 5xULN with liver involvement)
Serum creatinine or creatinine clearance (CrCl)	≤ 1.5 x ULN or CrCl ≥ 50 mL/min by Cockcroft-Gault Formula
Total Bilirubin	≤ 2.0 x ULN

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Any concurrent condition requiring the continued or anticipated use of systemic steroids beyond physiologic replacement dosing (excluding non-systemic inhaled, topical skin, nasal, and/or ophthalmic corticosteroids). All other systemic corticosteroids above physiologic replacement dosing must be discontinued at least four weeks prior to first study treatment.
2. Treatment with another investigational drug or other intervention within four weeks prior to the first study treatment date.
3. Treatment with trans-arterial liver embolization, hepatic arterial infusion, or radiation doses of > 30 Gy within 4 weeks prior to the first study treatment date
4. Treatment with chemotherapy within 3 weeks prior to the first study treatment date
5. History of permanent discontinuation of a PD-1 or PD-L1 inhibitor therapy due to an immune related adverse event.
6. Prior treatment with a CTLA-4 inhibitor
7. Pregnant or breastfeeding
8. Known allergic reactions to study drug components.
9. Active brain metastases. Patients with brain metastases must have stable neurological status following local therapy (surgery or radiation) for at least four weeks prior to first study treatment and must be off steroids related to the brain metastases for at least two weeks prior to study treatment.
10. Active drug or alcohol use or dependence as documented in the chart that, in the opinion of the investigator, would interfere with adherence to study requirements.
11. Active bacterial, viral, parasitic, or fungal infection requiring IV therapy within 2 weeks of the start of protocol treatment.
12. A secondary primary malignancy that, in the judgement of the investigator, may affect the interpretation of results.
13. Prior organ allograft or allogeneic bone marrow transplantation.
14. A history of, or active, pneumonitis or interstitial lung disease.
15. Active autoimmune disease. Patients with vitiligo, type 1 diabetes mellitus, endocrinopathies manageable by hormone replacement, and psoriasis not requiring systemic treatment are permitted to enroll. Other autoimmune conditions may be

allowable at the discretion of the principal investigator.

16. Receipt of a live-virus vaccine within 30 days prior to first dose of study drug (seasonal flu and COVID-19 vaccines are permitted, as long as they do not contain live virus and are not administered within 24 hours of planned administration of XmAb20717)
17. Known human immunodeficiency virus (HIV) infection with CD4+ T-cell (CD4+) counts < 350 cells/μL, or an HIV viral load greater than 400 copies/mL, or a history of an acquired immunodeficiency syndrome (AIDS)-defining opportunistic infection within the past 12 months, or who has not been on established antiretroviral therapy (ART) for at least 4 weeks prior to initiation of study drug dosing. (Effective ART is defined as a drug, dosage, and schedule associated with reduction and control of the viral load. HIV positive subjects who do not meet any of these exclusion criteria are eligible.)
18. Any serious or uncontrolled medical or psychiatric disorder that, in the opinion of the investigator, would prevent the patient from providing informed consent, may increase the risk associated with study participation or study drug administration, impair the ability of the patient to receive study protocol therapy, or interfere with the interpretation of the study results.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but have not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because they temporarily meet an exclusion criterion, may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 Strategies for Recruitment and Retention

Patients will be identified through the clinical practices of the Abramson Cancer Center and the Hospital of the University of Pennsylvania and its affiliated hospitals and through referrals from outside hospitals and physicians. The trial will be publicized on the websites of the Abramson Cancer Center and the Hospital of the University of Pennsylvania. This protocol will also be listed in the ClinicalTrials.gov database. Patients will be required to give written consent to participate before any screening tests or evaluations are conducted.

Vulnerable populations such as pregnant women, prisoners, children, cognitively impaired participants lacking consent capacity, and employee volunteers will not be

eligible for participation in this research study and will not be recruited.

6 STUDY INTERVENTION

6.1 Study Intervention(s) Administration

6.1.1 Study Intervention Description

XmAb20717 is a humanized bispecific antibody that binds both PD-1 and CTLA4 as described in section 2.2.2.

6.1.2 Dosing and Administration

A dose of 10mg/kg will be administered intravenously on days 1 and 15 of each 28 day cycle. Intravenous administration will occur over 1 hour (± 10 minutes).

Clinical experience with XmAb20717 is limited. Caution should be exercised as infusion reactions, allergic reactions, or other unexpected reactions may occur.

XmAb20717 administration should begin as soon as possible after the dosing solution is made. If there is a delay in administration, the dosing solution may be stored at 2°C to 8°C for no more than 24 hours or at room temperature for no more than 4 hours prior to infusion. The full calculated dose will be administered based on the participant's actual baseline weight measurement in kilograms. Following the first dose, subsequent doses will be modified only if the participant's weight changes by more than 10% from the baseline (Day -1 or Day 1, assessment closest to the first dose) weight, at which point the dose will be recalculated using the current weight.

XmAb20717 SHOULD NOT BE ADMINISTERED AS AN IV PUSH OR BOLUS.

XmAb20717 will be administered as an open-label solution at a constant rate over a 1-hour period (± 10 minutes). Precautions for infusion reactions/anaphylaxis should be observed during XmAb20717 administration. Due to the possibility that allergic/infusion reactions may occur, emergency resuscitation equipment (a "crash cart") should be present in the immediate area where participants are receiving their infusions. Additional supportive measures should be available and may include, but are not limited to, acetaminophen, antihistamines, corticosteroids, IV fluids, bronchodilators, epinephrine, vasopressors, diphenhydramine, and oxygen.

All supportive measures consistent with optimal patient care will be provided throughout the study according to institution standards.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Acquisition and accountability

XmAb20717 will be supplied by The Almac Group. XmAb20717 will be stored by the Investigational Drug Service per the guidelines noted in section 6.2.3 below.

Detailed instructions and procedures for study treatment (XmAb20717) dispensing are included in the Pharmacy Manual.

Accurate accounting of all study treatment must be maintained. The Principal Investigator agrees to keep an inventory of study treatments using local investigational pharmacy drug accountability logs. Drug disposition records must be kept in compliance with applicable guidelines and regulations.

These records shall include dates, quantities, batch numbers, expiration dates, and the unique code numbers assigned to the study treatment and to the study participants.

The Investigator shall be responsible for ensuring records that adequately document that the participants who were provided the doses specified in the protocol and that all study treatment received from the Sponsor are reconciled.

Upon completion or termination of the study, any used or partially used vials and unused study medication or diluted drug dosing solutions should be destroyed in compliance with local investigational pharmacy policies or returned to the Sponsor or its designee.

6.2.2 Formulation, Appearance, Packaging, and Labeling

XmAb20717 will be supplied in single-use glass vials. Each 10 mL vial is filled with 10.0 mL of drug product containing 10.0 ± 1.0 mg/mL of XmAb20717 in 20 mM histidine, 250 mM sorbitol, and 0.01% (w/v) polysorbate-80 at pH 6.2. Each product vial is intended to deliver 10.0 mL of drug solution. XmAb20717 will be packaged and labeled according to applicable local and regulatory requirements.

XmAb20717 containing vials should appear as a transparent liquid free of particulate matter and/or discoloration. **Prior to dilution, the vial containing parenteral drug product should be inspected visually. If particulate matter and/or discoloration are noted, drug should not be administered, and the Sponsor should be notified.**

6.2.3 Product Storage and Stability

Vials containing XmAb20717 must be stored under refrigeration at 2°C to 8°C in an appropriately secured area accessible only to the pharmacist, the Principal Investigator,

or a duly designated person. Since XmAb20717 does not contain preservatives, opened vials of XmAb20717 must be used within 24 hours.

6.2.4 Preparation

Note that each XmAb20717 product vial must be diluted before administration.

Prior to administration, XmAb20717 will be diluted to the required final concentration in an ethylene/polypropylene copolymer infusion bag containing 0.9% Sodium Chloride Injection, United States Pharmacopeia, and the vial containing parenteral drug product should be inspected visually. If particulate matter and/or discoloration are noted, drug should not be administered, and the Sponsor should be notified. After dilution, the bag containing XmAb20717 should be gently inverted 2 to 3 times to mix the solution. **THE BAG MUST NOT BE SHAKEN**; excess agitation may cause aggregate formation. See the XmAb20717 Pharmacy Manual for additional details.

6.3 Measures to Minimize Bias: Randomization and Blinding

Not applicable

6.4 Study Intervention Compliance.

Adherence to intravenous infusion with XmAb20717 will be directly observed and recorded in the electronic health record and the electronic case report form (eCRF) with each research infusion visit.

6.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the eCRF are concomitant prescription medications, over-the-counter medications and supplements. Medications will be reported in the eCRF per the SoA in Appendix 12.1.

As stated in the exclusion criteria in section 5.2, participants will not be permitted to enroll in the study if, prior to study intervention, they require the use of systemic steroids beyond physiologic replacement dosing.

No concomitant cancer therapeutics may be administered during treatment with XmAb20717, excluding adjuvant hormonal therapy for breast or prostate cancer.

6.5.1 Rescue Medicine

Due to the possibility that allergic/infusion reactions may occur, emergency resuscitation equipment (a "crash cart") should be present in the immediate area where participants are receiving their infusions. Additional supportive measures will be available and may include, but are not limited to, acetaminophen, antihistamines, corticosteroids, IV fluids, bronchodilators, epinephrine, vasopressors, diphenhydramine, and oxygen.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation from XmAb20717 treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event.

Withholding or discontinuation of XmAb20717 due to irAEs should be guided by the NCCN guidelines for the management of immunotherapy related toxicities, outlined in Appendix 12.2, though the ultimate decision is at the discretion of the treating clinician and principal investigator. When XmAb20717 is held for toxicity (and not permanently discontinued), it may be reinitiated when AEs return to baseline or Grade $\leq$ 1. Exceptions to this may be permissible if deemed appropriate by the principal investigator. If XmAb20717 is interrupted for more than 12 weeks, treatment should be discontinued unless continuation is approved by the principal investigator.

For any toxicity of XmAb20717 (regardless of grade) that, despite optimal supportive care, is felt by the treating investigator to present a risk to safety of the study patient, additional treatment delay or treatment discontinuation is permitted at the discretion of the treating investigator.

XmAb20717 will be discontinued after two years of treatment for patients remaining on treatment at that time. Patients who completed two years of XmAb20717 treatment but experience disease progression after treatment discontinuation will be permitted to re-initiate treatment with XmAb20717.

The data to be collected at the time of study intervention discontinuation will include the following:

- Review of adverse events
- Targeted physical examination
- Vital signs and weight

- ECOG performance status
- Lab testing including CBC with diff, CMP, and TSH with reflex free T4

- Tumor imaging

Further detail is presented in the Schedule of Activities in Appendix 12.1.

After study treatment discontinuation, patients will have safety follow up for 90 days after treatment discontinuation for immune-related adverse events. Subsequently, patients will be followed within the medical record or have telephone follow up every 6 months to complete two years as documented in the SoA in Appendix 12.1.

7.2 Participant Discontinuation/Withdrawal from the Study

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant non-compliance with XmAb20717 treatment
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Disease progression which requires discontinuation of XmAb20717 treatment
- If the participant meets an exclusion criterion, not previously recognized, that precludes further study participation
- Participant unable to receive XmAb20717 for 12 weeks.

The reason for participant discontinuation or withdrawal from the study will be recorded on the eCRF. Patients who sign the informed consent form but do not receive the study intervention may be replaced. Patients who sign the informed consent form and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study at a point where they are not considered evaluable for efficacy endpoints per section 8.3.2 will be replaced.

7.3 Lost To Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit and counsel the participant on the importance of maintaining the assigned visit

schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENT AND PROCEDURES

8.1 Schedule of Study Procedures

A schedule of study procedures is provided in Appendix 12.1 and procedures to occur at each visit is discussed below.

Study procedures, including research collections and visits, that are missed due to SAEs will not be considered deviations and will be omitted. In other words, the study calendar will not be "paused" at the time of SAEs but will continue on and patients will resume scheduled study procedures when able without "making up" omitted study procedures.

Visit 1 (Day -28 to 0)	Screening
• Obtain informed consent • Screen potential participants by inclusion and exclusion criteria • Obtain complete medical history and demographics, document • Prior and concomitant medication review • Tumor imaging of abdomen with CT or MRI, CT or MRI of pelvis, and CT chest within 28 days of the start of study therapy • Collection of labs including pregnancy test, CBC with diff, CMP, TSH with reflex free T4, CA-19-9, and CEA • Archival or fresh tumor biopsy • Physical exam, vital signs, height, weight and ECOG performance status	
Visit 2 (Day 1)	Treatment initiation
• Treatment with XmAb20717 • Prior and concomitant medication review • Physical exam, vital signs, weight, and ECOG performance status • Baseline adverse events assessment • Labs including CBC with diff, CMP, TSH with reflex free T4, CA19-9, and CEA (CA-19-9 should only be measured on an ongoing basis if abnormal at baseline. CEA should only be measured on an ongoing basis if abnormal at baseline and CA 19-9 normal at baseline) • Peripheral blood testing for correlative studies drawn prior to treatment initiation	

Visit 3 (Day 8)	Visit for correlative evaluation (lab visit)
• Peripheral blood assessment for correlative studies	
Visit 4 (Day 15)	Treatment visit
• Treatment with XmAb20717 • Prior and concomitant medication review • Physical exam, vital signs, weight, and ECOG performance status • Review adverse events • Labs including CBC with diff, CMP, TSH with reflex free T4 • Peripheral blood assessment for correlative studies	
Day 1 and Day 15	Treatment visits cycle 2 and beyond
• Treatment with XmAb20717 • Prior and concomitant medication review • Physical exam, vital signs, weight, and ECOG performance status • Review adverse events • Labs including CBC with diff, CMP, TSH with reflex free T4 • Tumor markers (CA 19-9 or CEA) should be checked on day 1 of each cycle if abnormal at baseline as above • Refer to Appendix Section 12.1, Schedule of Activities for additional interventions including peripheral blood assessment for correlative studies and tumor imaging	
End of treatment visit (can be conducted during a scheduled office visit, such as to review scans demonstrating progression, or separately)	Treatment discontinuation assessments
• Review adverse events • Targeted physical examination and ECOG performance status • Lab testing including CBC with diff, CMP, TSH with reflex free T4 • Tumor markers (CA 19-9 or CEA) if abnormal baseline as above. • Tumor imaging if not performed in the prior 28 days	
30 and 90 days after last infusionwith XmAb20717	Safety follow-up
• Phone call or office visit with nurse to review adverse events	
Every 6 months to complete 2 years from the end of treatment	Follow-up

- Survival status assessment via medical records or by telephone
- Post-study anti-cancer therapy status via medical records or by telephone

8.2 Study Evaluations and Measurements

8.2.1 Inclusion and exclusion criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that participant qualifies for the trial.

8.2.2 Informed consent

The investigator must obtain documented consent from each potential participant prior to enrollment in the clinical trial. Study specific procedures should not be conducted until a patient has provided consent, but testing obtained as standard of care prior to consent such as laboratory values and imaging may be used for study eligibility.

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on the consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant prior to participation in the trial.

The initial consent form, any subsequent revised written informed consent form, and any written information provided to the participant must receive the IRB's approval/favorable opinion in advance of use. The participant and their legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

8.2.3 Medical history and demographic data

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions and any conditions diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. This review will occur at study visits noted in the SoA in Appendix 12.1. Details regarding the disease forwhich the participant has been enrolled in this study will be recorded separately and not listed as medical history. Demographic data collected will include sex, date of birth, and race/ethnicity.

8.2.4 Prior and concomitant medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days prior to trial initiation. The following details will be collected: drug name, reason for treatment, dose/units, route of administration, frequency, start and end date of therapy.

Treatment for the disease for which the participant has enrolled on the trial will be recorded separately and will not be listed under prior medication.

Patients must be instructed not to take any medications, including over-the-counter products such as vitamins, minerals and other dietary supplements, without first consulting the Investigator. All concomitant medications must be recorded on the relevant eCRF.

Supportive care and other medication, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the investigator and recorded in the relevant eCRF.

The investigator or qualified designee will record medication taken by the participant during the trial. Review of prior and concomitant medications will occur during study visits indicated in the SoA in Appendix 12.1.

8.2.5 Cancer history and disease status

The investigator or qualified designee will obtain details on the patient's cancer diagnosis including site, date of diagnosis, stage, sites of metastatic disease, and prior anti-cancer treatment including surgery, systemic therapy, and radiation therapy.

8.2.6 Vital Signs

The investigator or qualified designee will assess and record vital signs at time points indicated in the SoA in Appendix 12.1. Vital signs should include temperature, pulse, respiratory rate, oxygen saturation, weight and blood pressure. Height need only be measured once at the main screening visit per the SoA in Appendix 12.1.

8.2.7 Full physical exam

The investigator or qualified designee will perform a complete physical exam during the main screening visit. Clinically significant abnormal findings should be recorded as medical history.

8.2.8 Targeted physical exam

For cycles that do not require full physical exam per the SoA in Appendix 12.1, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to treatment administration as determined by the investigator or directed by patient complaints.

8.2.9 ECOG performance status

ECOG performance status will be measured at specified visits in the SoA in Appendix 12.1 according to Table 8 in Appendix 12.4.

8.2.10 Laboratory Evaluations

Blood samples will be taken to be tested in the clinical laboratory at intervals specified in SoA in Appendix 12.1.

Complete Blood Count:
White blood cell (WBC) count with differential, hemoglobin, hematocrit, and platelet count

Serum Chemistry:
Sodium (Na), potassium (K), chloride (Cl), bicarbonate (HCO3), calcium (Ca), blood urea nitrogen (BUN), creatinine (Cr), total bilirubin(Tbili), alkaline phosphatase (ALP), AST, ALT, albumin (Alb)

Tumor Markers:
CA19-9 and CEA. CA19-9 will be repeated per SoA in Appendix 12.1 only if abnormal at screening. CEA will be repeated per SoA in Appendix 12.1 only if abnormal at screening AND CA19-9 is normal at screening.

Thyroid Stimulating Hormone (TSH):
Thyroid stimulating hormone (TSH); if abnormal, check free T4

8.2.11 Pregnancy Testing

A serum pregnancy test will be performed at specified visits per SoA in Appendix 12.1 for female patients of reproductive potential.

Women are considered to be of childbearing potential unless it is documented that they are over the age of 60 OR postmenopausal by history with no menses for 1 year and confirmed by follicle-stimulating hormone (using local reference ranges) OR have a history of hysterectomy and/or bilateral oophorectomy OR have a history of bilateral tubal ligation.

Female subjects of childbearing potential must agree to use a highly effective method of birth control during and for at least 3 months after the last study dose of XmAb20717. Male subjects with female partners of reproductive potential must agree touse a highly effective method of birth control during and for 4 weeks after completion of the study (the last dose of XmAb20717 administered). Additionally, male subjects must agree to not donate sperm during and for 4 weeks after the completion of the study.

Highly effective methods of birth control for women include hormonal birth control (oral,

intravaginal, or transdermal), or progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or intrauterine), intrauterine devices (IUDs), intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner (provided partner is the sole sexual partner and there has been a medical assessment of surgical success), or sexual abstinence. For men on the study, highly effective methods of birth control include vasectomy (provided there has been a medical assessment of surgical success), or a condom in combination with double barrier methods, spermicide, hormonal birth control, or IUD used by the female partner. The list of methods above is not exhaustive and additional contraception methods may also be acceptable if approved by the study doctor.

8.3 Efficacy Assessments

8.3.1 Antitumor effect

For the purpose of this study, patients will be evaluated for response every 8 weeks for 24 weeks and then every 12 weeks thereafter by CT scan of the chest with or without contrast and CT scan and/or MRI of the abdomen with IV contrast (pelvis required only if disease documented in pelvis on baseline scan). The same imaging modality should be used throughout the study if possible. Baseline scans of the chest, abdomen, and pelvis must obtained within 28 days of the start of study therapy.

8.3.2 Definition of evaluable

Evaluable for toxicity: All patients will be evaluable for toxicity from the time of their first treatment with XmAb20717.

Evaluable for efficacy endpoints, including overall response: Only those patients who have measurable disease present at baseline, have received at least two infusions (one cycle) of XmAb20717, and have had their disease re-evaluated by appropriate imaging after at least 4 and no more than 12 weeks from cycle 1 day 1 will be considered evaluable for efficacy endpoints including overall response. These patients will have their response classified according to the definitions stated below. Patients will be evaluable for the overall survival endpoint if they have received at least two infusions (one cycle) of XmAb20717, even if repeat imaging not performed.

Patients who are not considered evaluable for ORR endpoint will be replaced.

8.3.3 Disease parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as >20 mm by chest x-ray, as >10 mm with CT scan, or >10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be >15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15mm short axis) are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target lesions: All measurable and/or evaluable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. In patients who have received locoregional therapy to the liver, lesions that have not been treated locally should be preferentially chosen as target lesions. If a liver lesion that has been treated using locoregional therapy must be chosen as a target lesion, progression of the lesion is required after locoregional therapy, A sum of the diameters (longest for non-nodal lesions,

short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline.

Measurements of these lesions are not required, but the presence, absence, or in rare cases, unequivocal progression, of each should be noted throughout follow-up.

8.3.4 Methods for evaluation of measurable disease

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

8.3.5 Response criteria

8.3.5.1 Evaluation of target lesions (RECIST 1.1)

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.3.5.2 Evaluation of non-target lesions

Non-target lesions should be followed and labeled as 'present', 'absent', or 'unequivocal progression', defined as an overall level of substantial worsening in non-target disease, such that even in the presence of stable disease or partial response in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. 'Unequivocal progression' of non-target disease will classify a patient has having progressive disease (PD).

8.3.5.3 Immune-related response in measurable lesions (iRECIST)

iRECIST guidelines were established in 2017 to guide response assessments in clinical trials testing immune-therapeutics. Full details of the iRECIST criteria for this study can be found in Seymour L et al, Lancet Oncology 2017.[26]

If initial RECIST 1.1-defined progression (ie, iUPD) is noted on imaging in the setting of clinical stability, patients may remain on study treatment and have confirmatory imaging in 4-8 weeks (study specified scans (every 8 or 12 weeks based on SoA in Appendix 12.2) should continue on initial schedule if patient remains on study). An assignment of clinical stability requires that no worsening of performance status has occurred, that no clinically relevant increases in disease-related symptoms such as pain or dyspnea occurthat are thought to be associated with disease progression, and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care. The imaging findings and the recommendation to continue with treatment despite iUPD should be discussed with the patient before a decision is made about whether or not to continue therapy. Patients whohave iUPD and are not clinically stable should be designated as not clinically stable in thecase report form. This designation will allow the best overall response to be calculated and the date of iUPD to be used in estimates of progression-free survival by iRECIST.

If radiologic progression is confirmed (iCPD), they will be determined to have progressive disease by iRECIST and discontinued from study therapy, but if repeat imaging shows stable disease or response by RECIST 1.1 they may remain on study therapy with imaging continuing as previously scheduled every 8 weeks for 24 weeks then every 12 weeks thereafter (cycle 3 day 1, cycle 5 day 1, etc.).

Table 2: Comparison of RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10mm in diameter (≥ 15mm for nodal lesions); maximum of five lesions	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are

	(two per organ); all other disease is considered non-target (must be ≥ 10 mm in short axis for nodal disease)	recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before CR, PR, or SD
New lesions	Results in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment, additional new lesions appear or an increase in size of new lesions is seen (≥ 5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST = Response Evaluation Criteria in Solid Tumors. iUPD = unconfirmed progression. iCPD = confirmed progression. iCR = complete response. iPR = partial response. iSD = stable disease.

Table 3: Assignment of timepoint response using iRECIST

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
Target lesions: iCR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change or decrease from last timepoint; new lesions: yes	Not Applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥ 5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD.
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)

Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ≥ 5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures ≥ 5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ≥ 5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in size or number of new lesions previously identified.

Target lesions, non-target lesions, and new lesions defined according to RECIST 1.1 principles (Section 8.3.3); if no pseudoprogression occurs, RECIST 1.1 and iRECIST categories for complete response, partial response, and stable disease would be the same.

*Previously identified in assessment immediately before this timepoint. “i” indicates immune responses assigned using iRECIST. iCR = complete response. iPR = partial response. iSD = stable disease. iUPD = unconfirmed progression. Non-iCR/non-iUPD = criteria for neither CR nor PD have been met. iCPD = confirmed progression. RECIST = Response Evaluation Criteria in Solid Tumors.

8.3.5.4 Overall response rate

Overall response rate (ORR) is defined as the proportion of patients who achieve a complete or partial response during the course of the study. The best response experienced by a patient (CR > PR > SD > PD) will be used. Responses will be determined by investigator review. The primary study endpoint will be use RECIST v. 1.1 definitions (sections 8.3.5.1 and 8.3.5.2) to define overall response rate. Overall response rate by iRECIST criteria (section 8.3.5.3) will be a secondary endpoint.

8.3.5.5 Duration of response

Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

8.3.5.6 Progression-free survival

PFS is defined as the duration of time from start of treatment to time of progression using RECIST v.1.1 criteria,[26] death, or last patient contact when progression-free. For patients who are progression-free, PFS will be censored at the most recent date which documents progression-free status (i.e., scan date or clinical visit date).

8.3.5.7 Overall survival

OS is defined as the duration of time from start of treatment to death due to any cause with censoring at last patient contact alive for patients who are lost to follow up or who do not experience the outcome of death during the study period. Public records (e.g. obituaries) may be used to ascertain dates of death for patients where such data is not available in the medical record unless the patient withdraws consent for follow-up. For patients who enroll in hospice care in whom the specific date of death cannot be determined, date of death will be recorded as the date the patient entered hospice.

8.3.6 Correlative studies

8.3.6.1 Correlative blood samples

Peripheral blood correlative studies will be performed at the time points noted in the SoA in Appendix 12.1. At each time point, 50 mL of blood will be drawn for correlative studies. Peripheral blood samples will be immediately sent to the Human Immunology Core (HIC) at the University of Pennsylvania and peripheral blood mononuclear cells (PBMCs) will be isolated. Samples will undergo multi-parameter flow cytometry performed by Dr. Huang's laboratory at the University of Pennsylvania.

8.3.6.2 Tumor biopsy

Archival tumor tissue, from diagnosis or more recent tumor biopsy, will be obtained to perform correlative studies. Next-generation sequencing will be obtained if not previously performed on archival tissue, if available, or re-biopsy should be performed as part of standard of care management to allow for next-generation sequencing. Samples will be analyzed by immunohistochemical staining (IHC) with markers including CD8, CD3, FoxP3, CK19, CD68, Ki-67, and PD-L1. Analysis will include counting the number of cells per 40X field staining positively for each marker with at least four fields examined for each marker.

8.4 Safety and Other Assessments

8.4.1 Toxicity evaluation

All patients entered into the study and who are given at least one dose of XmAb20717 will have detailed information collected on adverse events for the overall study safety analysis. All adverse events will be categorized and tabulated using CTCAE v. 5.0.

8.5 Adverse Events and Serious Adverse Events

8.5.1 Definition of Adverse Events (AE)

An adverse event (AE) is any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention related. Intercurrent illnesses or injuries should be regarded as adverse events.

A pre-existing condition should be recorded as an adverse event if the frequency, intensity or the character of the condition changes.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.
- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires active management.

8.5.2 Definition of Serious Adverse Events (SAE)

Serious Adverse Events (SAE)

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that, in the view of the investigator, is:

- fatal

- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes.

Important medical events are those that may not be immediately life threatening but are clearly of major clinical significance. They may jeopardize the patient and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious should be regarded as non-serious adverse events.

8.5.3 Classification of an Adverse Event

8.5.3.1 Severity of Event

All AE's will be categorized and graded using CTCAE v. 5.0.

8.5.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to the study intervention assessed by the Investigator who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be considered.

- Definitely Related – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to the study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal

laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- Possibly Related – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unrelated – The AE is completely independent of the study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.5.3.3 Expectedness

The principal investigator will be responsible for determining expectedness; and the latest approved IB-RSI will be used.

8.5.4 Time Period and Frequency for Event Assessment and Follow-Up

Safety will be assessed by monitoring and recording potential adverse effects using the CTCAE v. 5.0 at each study visit. Participants will be monitored by medical histories, physical examinations, and laboratory studies as outlined in Appendix 12.1 SoA. If CTCAE v. 5.0 grading does not exist for an adverse event, the severity of mild, moderate, severe, life-threatening, and death, corresponding to Grades 1-5, will be used whenever possible.

At each contact with the patient, the investigator will seek information on adverse events by non-directive questioning and, as appropriate, by examination. Adverse events may also be detected when they are volunteered by the patient during the screening process or between visits, or through physical examination, laboratory test, or other assessments. Information on all adverse events will be recorded in the source documentation. To the extent possible, adverse events will be recorded as a diagnosis and symptoms used to make the diagnosis recorded within the diagnosis event.

As much as possible, each adverse event or follow-up information will be evaluated to determine:

1. Severity grade (CTCAE Grade 1-5)
2. Duration (start and end dates)
3. Relationship to the study treatment or process – Reasonable possibility that AE is related: No (unrelated/ not suspected) or Yes (a suspected adverse reaction). If

yes (suspected) - is the event possibly, probably or definitely related to the investigational treatment?
4. Expectedness to study treatment or process – Unexpected – if the event severity and/or frequency is not described in the RSI section of the investigator brochure.
5. Action taken with respect to study or investigational treatment or process (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)
6. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)
7. Whether the event is serious

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

8.5.5 Adverse Event Reporting

Reporting Period
Adverse events will be reported from the beginning of the reporting period (defined as time of first study treatment) until the end of the reporting period (defined as 30 days after the last XmAb20717 infusion for patients in whom XmAb20717 treatment is permanently discontinued, initiation of another anti-cancer therapy, or withdrawal of consent by participant, whichever occurs first).

Immune related adverse events will be reported from the time of first study treatment until 90 days after the last XmAb20717 infusion (for patients in whom XmAb20717 treatment is permanently discontinued) or withdrawal of consent by participant, whichever occurs first.

During the the screening period (prior to the beginning of the reporting period) and the follow-up period (after the end of the reporting period defined above), adverse events, including SAEs, that are unrelated to study treatment do not need to be reported.

Investigator Reporting: Notifying Xencor
Fatal drug-related SAEs should be reported to Xencor within the next business day after the day of awareness of the event.

Life-threatening drug-related SAEs should be reported to Xencor within three business days of Principal Investigator's determination of event and no later than five business days from the day of awareness of the event.

Drug-related non-life-threatening and non-fatal SAEs should be reported to Xencor within seven (7) calendar days after the day of awareness of the event.

All other reportable information (overdose, newly diagnosed cancer, exposure during

pregnancy or lactation, non-drug related SAEs and cases of Potential Drug-Induced Liver Injury where the subject was exposed to the Xencor product) should be reported to Xencor within 10 calendar days after the day of awareness of the event

For patients in screening (prior to the beginning of the reporting period) or those in follow-up after the end of the reporting period defined in Reporting Period above, only SAEs potentially related to XmAb20717 or study procedures will be reported.

Recurrent episodes, complications, or progression of the initial SAE must be reported to Xencor as a follow-up to the original episode within 2 business days of the investigator receiving the follow-up information. A SAE considered completely unrelated to a previously reported one should be reported separately as a new event.

Send the SAE report to the icon-mads@iconplc.com.

New information regarding the SAE will be reported as it becomes available and in the same manner that the initial SAE (i.e. SAE form). The investigator must follow the event to resolution or until the event is deemed and documented irreversible, whichever is longer.

All non-serious AEs should be compiled as an Excel spreadsheet derived from the clinical database quarterly (the first day of each quarter) and emailed to Xencor's pharmacovigilance group (ma.pv@xencor.com) unless there is critical and important information that should be reported to Xencor as soon as possible. If an AE requires action by Xencor to prevent unreasonable risk of substantial harm to the public health, then notice of such event shall be given by telephone to Xencor and emailed to Xencor (ma.pv@xencor.com) as soon as possible.

Investigator Reporting: Local Reporting Requirements
The investigator will report AEs and SAEs to the IRB/EC of record and other local regulatory groups per the local requirements.

8.5.6 Serious Adverse Event Reporting

The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected serious adverse reactions (fatal or life-threatening suspected adverse reactions within 7 calendar days and all other serious adverse reactions within 15 calendar days) per applicable regulations. In addition, the study sponsor must notify FDA and all participating investigators of potential serious risks, from XmAb20717 clinical trials or any other source, as per the applicable regulation.

8.5.7 Reporting Events to Participants

If an event occurs that requires change to the study consent form, patients will be notified and re-consented prior to continued study participation. Otherwise, individual AEs and

SAEs will not be reported to other patients.

8.5.8 Events of Special Interest

Not applicable.

8.5.9 Reporting of Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug or process may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a patient or patient's female partner, and the fetus is exposed to study drug and/or process (maternally or paternally), the following procedures should be followed to ensure patient safety:

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. The pregnancy should be reported to Xencor within 10 calendar days after the day of awareness of the event.

8.6 Unanticipated Problems

8.6.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.6.2 Unanticipated Problem Reporting

Unanticipated problems (UPs) such as:

- Post-marketing withdrawal of a drug, device, or biologic used in a research protocol due to safety concerns.
- FDA ban of a drug, device, or biologic used in a research protocol due to safety concerns.
- Complaint of a participant when the complaint indicates unexpected risks, or the complaint cannot be resolved by the research team
- Breach of confidentiality
- Incarceration of a participant when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the patient to remain on the study
- Premature closure of a study (e.g., due safety, lack of efficacy, feasibility, financial reasons, etc.)

should be reported by the investigator to the Sponsor, reviewing Institutional Review Board (IRB) and to the lead principal investigator (PI). The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;

- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported as any other SAE.
- Any other UP will be reported to the Sponsor and IRB within 10 business days of the investigator becoming aware of the problem.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 10 business days of the IRB's receipt of the report of the problem from the investigator.

8.6.2.1 Reporting Unanticipated Problems To Participants

If unanticipated problem results in a change to the consent form, all patients on study will be re-consented. If unanticipated event results in closure of the study, patients on-study will be alerted on an individual basis.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical Hypotheses

Primary Efficacy Endpoint(s): Overall response rate (ORR) by investigator review using RECIST v. 1.1 (binary). The null hypothesis is an ORR of 5% and the one-sided alternative hypothesis is that the ORR will be greater than 5%.

Secondary Endpoint(s):

- Toxicity rates will be assessed as ordinal measures (e.g., Grade 1 pneumonitis, Grade 2 pneumonitis, etc.) using CTCAE v. 5.0. Toxicity rates will also be assessed as a binary measure of proportion of patients experiencing each toxicity.
- Overall response rate (ORR) using iRECIST criteria (binary variable)
- Progression free survival (PFS) (time to event variable)
- Duration of response (DOR) (time to event variable)
- Overall survival (time to event variable)

9.2 Sample Size Determination

Sample size determination is made on the basis of the primary outcome of ORR by RECIST v. 1.1. We will perform a Simon two-stage mini-max design. The null ORR is 5% based on a 5% ORR for standard-of-care second line therapy with FOLFOX and ORRs of 3 – 7% observed in phase II trials of single agent immune check point inhibitor therapy with PD-1 and PD-L1 inhibitors.[6,8–10] The null hypothesis will be tested against a one-sided alternative. In the first stage, 13 patients evaluable for efficacy will be accrued. If no

responses are observed in these 13 patients, the study will be stopped for futility. Otherwise, 14 additional patients evaluable for efficacy will be accrued for a total of 27 evaluable patients. If 4 or more responses are observed in 27 evaluable patients, then the null hypothesis will be rejected. This design yields a type I error rate of 0.05 and a power of 80% when the true ORR is 20%.[27]

9.3 Populations for Analyses

9.3.1 Efficacy Analysis

To be eligible for efficacy endpoints (ORR, PFS, DOR, and OS), patients must have completed at least one cycle of therapy (two infusions). To be evaluable for ORR, PFS, and DOR patients must also have had their disease re-evaluated by appropriate cross-sectional imaging (CT or MRI) at least 4 weeks and no more than 12 weeks after their baseline imaging. Patients who do not meet criteria for the ORR efficacy analysis will be replaced.

9.3.2 Safety Analysis

All patients entered into the study, who are given at least one dose of XmAb20717 will have detailed information collected on adverse events for the overall study safety analysis.

9.4 Statistical Analyses

9.4.1 General Approach

The primary endpoint of ORR by RECIST v. 1.1 and other binary endpoints will be summarized as binomial proportions with 95% confidence intervals. This includes the secondary endpoint of ORR within subgroups of patients defined by receipt of prior immune checkpoint inhibitor therapy. Time to eventendpoints including PFS, DOR, and OS will be analyzed using Kaplan Meier methods and will be summarized using medians with 95% confidence intervals. Adverse events will be summarized as binomial proportions with 95% confidence intervals.

Baseline clinical and demographic characteristics will be summarized using mean and standard deviation for continuous variables and as a proportion of patients falling into each category for categorical variables.

9.4.2 Analysis of the Primary Efficacy Endpoint(s)

As stated in section 9.2, the study will proceed via a Simon two-stage mini-max design. In the first stage, 13 patients evaluable for ORR will be accrued. If no responses are observed in these 13 patients, the study will be stopped for futility. Otherwise, 14 additional patients evaluable for ORR will be accrued for a total of 27 evaluable patients. If 4 or more responses are observed in 27 evaluable patients, then the null hypothesis will be rejected. This methodology is based on using a one-sided alternative hypothesis for ORR compared to a null hypothesis ORR of 5% using a binomial exact test with a typeI

error rate of 0.05.

9.4.3 Analysis of the Secondary Endpoint(s)

Secondary endpoints will be summarized as noted in section 9.4.1 and will not undergo formal statistical testing.

9.4.4 Safety Analyses

All adverse events will be categorized by CTCAE v. 5.0, tabulated as ordinal (Grade 1 through Grade 5), and summarized as binomial proportions (proportion of patients experiencing each event). Adverse events leading to discontinuation of therapy, serious adverse events, and adverse events of Grade 3 or higher will also be presented as binomial proportions.

9.4.5 Baseline Descriptive Statistics

Descriptive statistics will be performed as noted in section 9.4.1.

9.4.6 Planned Interim Analyses

Planned interim analysis is described in section 9.4.2.

9.4.7 Sub-Group Analyses

Any sub-group analyses performed will be exploratory in nature as the study will not be powered to assess differences in outcomes between sub-groups. This includes the secondary analysis examining ORR within subgroups of patients defined by prior receipt of immune checkpoint inhibitor therapy.

9.4.8 Tabulation of Individual Participant Data

Individual participant outcome data may be presented in a de-identified fashion, for example, in the form of swimmer's plots or waterfall plots to provide a visual summary of the depth and duration of clinical responses.

9.4.9 Exploratory Analyses

Analysis of immune markers in tissue and blood will be a hypothesis-generating exploration of potential predictive biomarkers.

Immunohistochemical markers (IHC) on tissue samples will be reported as number of cells staining for each marker per 40X field (with at least 4 fields examined, continuous variable) and as a proportion of examined cells that stain positive for the marker from the total number of cells examined (proportion). Individual IHC markers may also be reported on an ordinal scale (e.g. 1+, 2+, 3+, etc.). If RNA sequencing is performed, normalized

gene expression for genes of interest will be calculated using a stably expressed gene and reported as a continuous variable. Multi-parameter flow cytometry for immune cell markers will be reported as a proportion of mononuclear cells represented by each cell type (proportion) and as a count of each cell type per volume of blood (continuous variable).

Logistic regression will be used to evaluate association of response status (binary) with baseline markers. Cox-proportional hazards regression models will be used to evaluate associations between exploratory markers and PFS, OS, and DOR.

To evaluate changes in blood markers with treatment, pre- and post-treatment comparisons will be made using paired, two-tailed t-tests with type I error rate of 0.05 for variables that can be treated as continuous variables (e.g., cell counts per unit volume, proportion of cell staining positive for IHC marker, ordinal reporting of IHC marker).

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Informed Consent Process

10.1.1.1 Consent/Assent and Other Informational Documents Provided To Participants

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to administering the study intervention. The following consent materials are submitted with this protocol: Patient Informed Consent Form.

10.1.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if

they decline to participate in this study.

10.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated by the Sponsor or the PI if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, funding agency, the Investigational New Drug (IND) sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

In terminating the study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the patients' interests.

10.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained

by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the Abramson Cancer Center in the Velos clinical trial database. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Abramson Cancer Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Abramson Cancer Center.

10.1.4 Future Use of Stored Specimens and Data

Data collected for this study will be analyzed and stored at the Abramson Cancer Center. After the study is completed, the de-identified, archived data will continue to be stored at the Abramson Cancer Center for use by other researchers including those outside of the study. Permission to use the de-identified data upon completion of the study will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the Abramson Cancer Center. These samples could be used to research the causes of advanced biliary tract cancer, its complications, and to improve treatment. The Abramson Cancer Center will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent regarding biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples may be provided through the Abramson Cancer Center.

10.1.5 Safety Oversight

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and

implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment, at least every 6 months, of the number and type of serious adverse events by an independent clinician, Roger Cohen, MD. Additionally, the Medical Monitor will be consulted for protocol exceptions and deviations and as needed for decision-making regarding dose modifications, study eligibility, and any need to stop enrollment or the study for safety concerns.

10.1.6 Clinical Monitoring

This study will be monitored in accordance with the Cancer Center's Clinical Trials Scientific Review and Monitoring Committee (CTSRMC) Plan, approved by NCI during the Core Grant's most recent review. This plan requires that the investigator submit a study-specific plan outlining how data will be reviewed. In addition, the CTSRMC plan calls for an internal audit by the Cancer Center's Data Safety Committee twice yearly.

The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

10.1.7 Quality Assurance and Quality Control

All monitoring and audits are to be performed according to ICH GCP E6(R2).

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the PI for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated, and specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.8 Data Handling and Record Keeping

10.1.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. All data requested on source documents must be recorded. All missing data must be explained. If a space on the source document is left blank because the procedure was not done, or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A.”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into the Velos data management system a 21 CFR Part 11-compliant data capture system provided by the Abramson Cancer Center. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents. Clinical and laboratory data will be entered into a 21 CFR Part 11-compliant electronic data capture system (EDC) that includes individual user account level password protection. This EDC (Velos version 9) supports programmable data entry validation rules and edit checks to identify data entry errors.

10.1.8.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an International Conference on Harmonization (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of XmAb20717. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.9 Protocol Deviations

The PI and the study team should document all scenarios where the protocol is not followed and provide, in particular:

- Who deviated from the protocol
- What was the deviation
- When did the deviation occur
- How did the deviation happen
- What is the impact of the deviation
- A root cause analysis of why the deviation occurred

If the assessment results in a determination that any of the following are potentially affected, the deviation would be considered of significant impact:

- having the potential to adversely affect patient safety; OR
- increases risks to participants; OR
- adversely affects the integrity of the data; OR
- violates the rights and welfare of participants, OR
- affects the patient's willingness to participate in research.
- there is a potential for an overall impact on the research that should be shared with the IRB for consideration and development of next best steps to address it

10.1.10 Publication and Data Sharing Policy

This study will comply with the data sharing agreement.

The Sponsor must approve all sharing of information/data prior to its occurrence.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the Principal Investigator. Any investigator involved with this study is obligated to provide the Principal Investigator with complete test results and all data derived from the study.

10.1.11 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 Additional Considerations

Not applicable

10.3 Protocol Amendment History

Version	Date	Description of Change	Brief Rationale
2.0	01/26/2022	Section 1.1 and Section 7.1 updated to reflect that study treatment will be discontinued at two years for patients who remain on therapy. For patients who complete two years of study treatment and experience disease progression after study treatment discontinuation, study treatment may be re-initiated	Clarify study treatment duration.
3.0	04/05/2022	Added additional correlative blood draws. Updated AE and SAE reporting to match CTA	Monitor longer term changes in immune system.
4.0	02/25/2023	Changed exclusion criteria to allow prior immune checkpoint inhibitor therapy. Added secondary analysis examining ORR within subgroups of patients defined by receipt of prior immune checkpoint inhibitor therapy. Clarified inclusion criteria to note that tumor sequencing results not required to enroll on the study. Clarified that study procedures not performed due to SAEs are omitted and are not considered deviations. Updated definition of AE/SAE reporting period and clarified that events outside of this reporting period only need to be reported if possibly related to study interventions or procedures.	Increasing population of patients receiving immune checkpoint inhibitor therapy as part of standard of care first-line therapy. Clarification of language surrounding inclusion criteria and contradictory language surrounding adverse event reporting.

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12 APPENDIX

12.1 Schedule of Activities (SoA)

All labs and study visits have a window of +/- 4 days. All imaging has a window of +/- 7 days

Table 3: Schedule of Activities

Study Phase	**Screening**	**Cycle 1 (28 days)**			**Cycles 2+ (28 days)**		**Post-treatment**		
Day	**-28 - 0**	**1**	**8**	**15**	**1**	**15**	**EOT**	**Safety follow-up[1]**	**Follow-up[2]**
Administrative Procedures									
Informed consent	X								
Inclusion/exclusion criteria	X								
Demographics and medical history	X								
Prior and concomitant medication review	X	X		X	X	X			
Trial treatment administration		X		X	X	X			
Post-study anticancer therapy status									X
Survival status									X
Clinical Procedures/Assessments									
Review adverse events	X	X		X	X	X	X		
Full physical examination	X								
Targeted physical examination		X		X	X	X	X		
Vital signs and weight	X	X		X	X	X	X		

ECOG performance status	X	X		X	X	X	X		
Laboratory procedures and assessments: Analysis performed by LOCAL laboratory									
Pregnancy test - serum beta HCG	X[3]								
CBC with differential	X	X		X	X	X	X		
Comprehensive metabolic panel	X	X		X	X	X	X		
TSH with reflex free T4	X				X		X		
Tumor Markers: CA19-9, CEA[4]	X				X		X		
Tumor imaging (CT or MRI)	X				X[5]		X		
Correlative studies blood collection		X	X	X	X[6]				
Tissue collection (archival or fresh biopsy if insufficient)[7]	X								

[1]Safety follow up via phone call or office visit will occur at 30 and 90 days after treatment discontinuation to evaluate immune-related adverse events.
[2]Follow up will be through review of the available medical record and/or phone calls every 6 months for up to 2 years.
[3]Pregnancy testing is applicable to women of reproductive potential defined in section 8.2.11.
[4]CA 19-9 should only be collected for subsequent blood draws if abnormal at baseline testing. CEA should be drawn only at baseline unless CA 19-9 normal and baseline CEA abnormal.
[5]Tumor imaging should occur prior to cycle 3 day 1, cycle 5 day 1, and cycle 7 day 1, then every 12 weeks or every third cycle thereafter (imaging every 8 weeks for 24 weeks then every 12 weeks thereafter). Imaging should include CT of the chest and MRI or CT of the abdomen +/- pelvis as documented in section 8.3.1.
[6]Correlative blood studies should be collected as indicated at cycle 1 day 1 prior to treatment, cycle 1 day 8, cycle 1 day 15, cycle 2 day 1, cycle 3 day 1, cycle 4 day 1, and cycle 5 day 1.
[7]Tissue biopsy (either archival or fresh) is required for confirmation of diagnosis prior to enrollment in the study

12.2 National Comprehensive Cancer Network Management of Immunotherapy-related toxicities

For a full reference of NCCN management guidelines for irAEs, see the NCCN Clinical Practice Guidelines in Oncology for the Management of Immunotherapy-Related Toxicities (Version 3.2021).[24]

Table 4: Dermatologic Adverse Event Management Algorithm

Adverse Event	Grade	Management
Maculopapular Rash	1	Continue immunotherapy Topical emollient Oral antihistamine for pruritus Treatment with moderate potency topical steroids to affected areas
	2	Continue immunotherapy Topical emollient Oral antihistamine for pruritus Treatment with moderate to high potency topical steroids to affected areas If unresponsive to topical, consider prednisone 0.5 mg/kg/day
	3 or 4	Hold immunotherapy Treatment with high potency topical steroids to affected areas Prednisone 0.5 – 1 mg/kg/day (increase dose up to 2 mg/kg/day if no improvement) Urgent dermatology consultation, consider biopsy Consider inpatient care
Pruritus	1	Continue immunotherapy Oral antihistamines Treatment with moderate potency topical steroids to affected areas or lidocaine patches for localized pruritus
	2	Continue immunotherapy with intensified antipruritic therapy Oral antihistamines Consider gabapentinoids (gabapentin, pregabalin) Treatment with high potency topical steroids to affected areas Dermatology consultation

Adverse Event	Grade	Management
	3	Hold immunotherapy Oral antihistamines Prednisone/methylprednisolone 0.5 – 1 mg/kg/day Consider gabapentinoids (gabapentin, pregabalin) Consider aprepitant or omalizumab for refractory cases Urgent dermatology consultation
Bullous dermatitis	1	Hold immunotherapy High potency topical steroids to affected areas
	2	Hold immunotherapy until < G1 Prednisone/methylprednisolone 0.5 – 1 mg/kg/day If no improvement after 3 days, consider adding rituximab
	3 or 4	Permanently discontinue immunotherapy Prednisone/methylprednisolone 1 – 2 mg/kg/day If no improvement after 3 days, consider adding rituximab or IVIG (1 g/kg/day in divided doses per package insert for 3 – 4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation
SJS or TEN	N/A	Permanently discontinue immunotherapy Prednisone/methylprednisolone 1 – 2 mg/kg/day Consider IVIG (1 g/kg/day in divided doses per package insert for 3 – 4 days) Inpatient care required Urgent dermatology, ophthalmology, and urology consultation

G1 = Grade 1; IVIG = intravenous immunoglobulin; N/A = Not Applicable; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrolysis.

Table 5: Gastrointestinal Adverse Event Management Algorithm

Adverse Event	Grade	Management
Diarrhea or Colitis	1	Consider holding immunotherapy Loperamide or diphenoxylate/atropine for 2 – 3 days • If no improvement and not already done, obtain labs for infectious workup Hydration Close monitoring • If persistent or progressive symptoms, check lactoferrin/calprotectin ○ If positive, treat as G2 (below) ○ If negative and no infection, continue G1 management and add mesalamine, cholestyramine
	2	Hold immunotherapy Prednisone/methylprednisolone (1 – 2 mg/kg/day) No response in 2 – 3 days, continue steroids, consider adding infliximab or vedolizumab within 2 weeks
	3 - 4	G3: Discontinue anti-CTLA4; consider resuming anti-PD1/PDL1 after resolution of toxicity# G4: Permanently discontinue immunotherapy agent responsible for toxicity Consider inpatient care for provision of supportive care IV methylprednisolone (1 – 2 mg/kg/day) • No response in 2 days, continue steroids, strongly consider adding infliximab or vedolizumab within 2 weeks

CTLA4= cytotoxic T-lymphocyte-associated protein; G = Grade; IV = intravenous; PD1 = programmed cell death protein 1; PDL1 = programmed cell death ligand 1.
#If G3 toxicity occurs, XmAb20717 should be permanently discontinued.

Table 6: Hepatic Adverse Event Management Algorithm

Adverse Event	Grade	Management
Transaminitis without elevated bilirubin	1 < 3 × ULN	Continue immunotherapy, consider holding immunotherapy for concerning lab value trend Assess transaminases and bilirubin with increased frequency
	2 3 – 5 × ULN	Hold immunotherapy Monitor LFTs every 3 – 5 days Consider prednisone 0.5 – 1 mg/kg/day
	3 5 – 20 × ULN	Hold immunotherapy Initiate prednisone 1 – 2 mg/kg/day; if steroid refractory or no improvement after 3 days, consider adding mycophenolate Consider inpatient care Monitor liver enzymes every 1 – 5 days depending on the magnitude and rate of change Hepatology consultation Infliximab should not be used for hepatitis
	4 > 20 × ULN	Permanently discontinue immunotherapy Initiate prednisone/methylprednisolone 1 - 2 mg/kg/day; if steroid refractory or no improvement after 3 days, consider adding mycophenolate Inpatient care Monitor liver enzymes daily Hepatology consultation Consider liver biopsy if no contraindications Infliximab should not be used for hepatitis
Grade > 1 transaminitis with bilirubin 1 - 3 × ULN (unless Gilbert's syndrome)	NA	Hold immunotherapy Initiate prednisone/methylprednisolone 1 – 2 mg/kg/day Consider inpatient care Monitor liver enzymes and LFTs every 2 – 3 days Hepatology consultation If steroid refractory or no improvement after 3 days, consider adding mycophenolate Infliximab should not be used for hepatitis

Adverse Event	Grade	Management
Grade > 1 transaminitis with bilirubin > 3 × ULN (unless Gilbert's syndrome)	N/A	Permanently discontinue immunotherapy Initiate prednisone/methylprednisolone 1 - 2 mg/kg/day Inpatient care Monitor liver enzymes daily Hepatology consultation If steroid refractory or no improvement after 3 days, consider adding mycophenolate Infliximab should not be used for hepatitis

LFT = liver function test; N/A = not applicable; ULN = upper limit of normal.

Table 7: Pancreatic Event Management Algorithm

Adverse Event	Grade	Management
Elevation in amylase/lipase (asymptomatic)	Mild ≤ 3 × ULN amylase and/or ≤ 3 × ULN lipase	If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy Evaluate for pancreatitis • Clinical assessment • Consider abdominal CT with contrast • Consider MRCP If evidence of pancreatitis, manage according to pancreatitis algorithm (below) Consider other causes for elevated amylase/lipase

	Moderate > 3 – 5 × ULN amylase and/or > 3 – 5 × ULN lipase	If isolated elevation of enzymes without evidence of pancreatitis, consider continuing immunotherapy Evaluate for pancreatitis • Clinical assessment • If persistent moderate to severe amylase and/or lipase elevation, abdominal CT with contrast or MRCP Consider other causes for elevated amylase/lipase If evidence of pancreatitis, manage according to pancreatitis algorithm (below)
	Severe > 5 × ULN amylase and/or > 5 × ULN lipase	If isolated elevation of enzymes without evidence of pancreatitis, consider continuing immunotherapy Evaluate for pancreatitis • Clinical assessment • If persistent moderate to severe amylase and/or lipase elevation, abdominal CT with contrast or MRCP Consider other causes for elevated amylase/lipase If evidence of pancreatitis, manage according to pancreatitis algorithm (below)
Acute pancreatitis	1	Consider gastroenterology referral IV hydration
		Manage as per elevation in amylase/lipase (asymptomatic; above)
	2	Hold immunotherapy Consider gastroenterology referral IV hydration Manage as per elevation in amylase/lipase (asymptomatic; above)
	3	Hold immunotherapy Gastroenterology referral Prednisone/methylprednisolone 0.5 - 1 mg/kg/day IV hydration

	4	Permanently discontinue immunotherapy Gastroenterology referral IV hydration Prednisone/methylprednisolone 1 – 2 mg/kg/day

CT =computed tomography; IV = intravenous; MRCP =magnetic resonance cholangiopancreatography; N/A = not applicable; ULN = upper limit of normal.

Table 8: Pulmonary Adverse Event Management Algorithm

Adverse Event	Grade	Management
Pneumonitis	1	Consider holding immunotherapy Reassess in 1 – 2 weeks • H&P • Pulse oximetry (resting and with ambulation) Consider chest CT with contrast
		• Consider repeat chest CT in 4 weeks or as clinically indicated for worsening symptoms
	2	Hold immunotherapy Consider pulmonary consultation Consider infectious workup: • Nasal swab for potential viral pathogens • Sputum culture (including bacterial, fungal, and acid-fast bacilli), blood culture, and urine antigen test (pneumococcus, legionella) Consider bronchoscopy with BAL (send for institutional immunocompromised panel) and consider transbronchial lung biopsy if clinically feasible Consider chest CT with contrast • Repeat chest CT in 3 – 4 weeks Consider empiric antibiotics (including coverage of atypical pathogens) if infection has not yet been fully excluded Prednisone/methylprednisolone 1 – 2 mg/kg/day Monitor every 3 – 7 days with: • H&P • Pulse oximetry (resting and with ambulation) If no improvement after 48 – 72 hours of corticosteroids, treat as Grade 3

	3 or 4	Permanently discontinue immunotherapy Inpatient care Infectious workup: • Consider that patient may be immunocompromised • Nasal swab for potential viral pathogens • Sputum culture (including bacterial, fungal, and acid fast bacilli), blood culture, and urine culture Pulmonary and infectious disease consultation
		Bronchoscopy with BAL (send for institutional immunocompromised panel) if feasible to rule out infection and malignant lung infiltration and consideration of transbronchial lung biopsy if feasible and clinically indicated Consider empiric broad-spectrum antibiotics (including coverage for atypical pathogens) if infection has not yet been fully excluded Methylprednisolone 1 – 2 mg/kg/day. Assess response within 48 hours and plan taper over ≥ 6 weeks Consider adding any of the following if no improvement after 48 hours: • Infliximab 5 mg/kg IV, a second dose may be repeated 14 days later at the discretion of the treating provider • IVIG • Mycophenolate mofetil 1 – 1.5 g BID then taper in consultation with pulmonary service

BAL = bronchoalveolar lavage; BID = twice a day; CT =computed tomography; H&P = history and physical; IV = intravenous; IVIG = intravenous immunoglobulin

Table 9: Renal Adverse Event Management Algorithm

Adverse Event	Grade	Management
Elevated serum creatinine/acute renal failure	1	Consider holding immunotherapy Follow creatinine and urine protein/creatinine ratio every 3 – 7 days Consider nephrology consult if creatinine remains unchanged over 2 weeks
	2	Hold immunotherapy Follow creatinine and urine protein/creatinine ratio every 3 – 7 days
		Nephrology consultation, consider renal biopsy if feasible prior to starting steroids Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out For persistent G2 beyond 1 week, prednisone/methylprednisolone 1 – 2 mg/kg/day
	3 or 4	Permanently discontinue immunotherapy Consider inpatient care Follow creatinine and urine protein/creatinine ratio every 3-7 days Nephrology consultation Consider renal biopsy if feasible prior to starting steroids Prednisone/methylprednisolone 1 – 2 mg/kg/day Consider adding one of the following if > G2 after 4-6 weeks of steroids: • Azathioprine • Cyclophosphamide (monthly) • Cyclosporine • Infliximab • Mycophenolate

G = grade.

12.3 ECOG Performance Status Table 10: ECOG

Performance Status

0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

END OF DOCUMENT